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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,251	11/20/2001	Timothy Guzi	IN0972K1B	2639

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER

HUANG, EVELYN MET

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 08/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

10/028,251

Applicant(s)

GUZI ET AL.

Examiner

Evelyn Huang

Art Unit

1625

-- Th MAILING DATE f this communication appears n the c ver sheet with the c rrespondenc address --

P r i d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) 24-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18,20-23 and 27-31 is/are rejected.
- 7) ☒ Claim(s) 19 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Priority

1. This application is the divisional of 09/465523. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Election/Restrictions

2. In response to the restriction requirement, applicant has elected group I wherein X is CH or C, claims 1-24, 27-31 in part, with traverse. Group II invention is withdrawn from further consideration as being drawn to the non-elected invention. An error occurs in the restriction requirement. Claims of Group I invention should be claims 1-23, 27-31 in part, because claim 24 is directed solely to the piperazinyl compound of Group II. A correction is hereby made.

Applicant argues that even though group I and group II compounds are distinct, they do share certain common structural features. However, because the group I invention, drawn to a piperidine and the group II invention, drawn to a piperazine, are structurally diverse compounds belonging to different classes and subclasses, a reference anticipating group I compounds would not render obvious the group II invention. The search is not co-extensive and is burdensome. The restriction as indicated is therefore proper. Furthermore, applicant has obtained a patent for the group II compounds. Deletion of the non-elected invention is recommended.

Claim Rejections - 35 USC § 112(2)

3. Claims 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

Art Unit: 1625

the invention. For these method claims, the subject to whom the compound is administered is missing but required.

Claim Rejections - 35 USC § 112(1)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18, 20-23, 27-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for the use of the compounds of claim 19 to inhibit ras farnesyl protein transferase, thereby inhibiting the farnesyl protein transferase -mediated abnormal growth of tumor cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following evaluation factors have been considered.

a. *Nature of the invention.*

The instant claims are drawn to a piperidinyl containing farnesyl protein transferase inhibiting tricyclic compounds and the method of using these compounds to inhibit abnormal growth of cells.

b. *State of the prior art/ level of the skill in the art.*

The protein farnesylation art is at its infancy stage. The development of inhibitors of farnesyl protein transferase has started recently in 1990. While protein farnesylation is linked to activation of ras protein, there is no nexus between inhibition of farnesyl protein transferase and (1) inhibition of abnormal growth of tumor cells wherein Ras protein is not activated; (2) inhibition of abnormal tumor cell growth wherein the ras oncogene is activated by a mechanism other than ras protein farnesylation; (3) inhibition of tumor cell growth wherein the Ras protein is activated as a result of oncogenic mutation in genes other than Ras oncogene; (4) inhibition of nontumor abnormal cell growth (Khosravi-Far, abstract).

The level of skill in the farnesyl protein transferase inhibitor art is high.

c. *Predictability/unpredictability of the art.*

Art Unit: 1625

The high degree of unpredictability is well known in the farnesyl protein transferase inhibitor art. A slight modification in the structure of the compound would drastically change its farnesyl protein transferase inhibiting activity as evidenced by the different IC_{50} values for farnesyl protein transferase of the structurally similar compounds (Bishop, 5719148, columns 347-374, Tables 7-8).

d. *Amount of guidance/working examples.*

The examples of instant piperidinyl compounds is limited to those wherein a is N, b,c, d are carbon, R9 being COO-t-butyl, and R8 being piperidinyl. The procedures for inhibition of farnesyl protein transferase and soft agar assay and the results for the piperazinyl compounds are described on pages 340-342 of the specification. Results for the instant piperidinyl compounds have not been described. No in vivo procedures are described.

e. *The breadth of the claims.*

Applicant's assertion that all the structurally diverse compounds, with aryl, heteroaryl or heterocyclyl further substituted with other bulky substituents that are encompassed by the generic claims would be effective in inhibiting abnormal growth of any type of cells in vitro or in vivo does not commensurate with the scope of the objective enablement, especially in view of (I) the fact that protein farnesylation art is at the infancy stage (paragraph b above); (ii) the high degree of unpredictability in the art (paragraph c above).

f. *Quantitation of undue experimentation.*

Since insufficient teaching and guidance have been provided in the specification (paragraphs c-e above), one of ordinary skill in the art, even with high level of skill, would not be able to use all the structurally diverse compounds to inhibit any type of abnormal cell growth as claimed without undue experimentation except for making and using the compounds of claim 19 to inhibit ras farnesyl protein transferase, thereby inhibiting farnesyl protein transferase-mediated abnormal growth of tumor cells.

Art Unit: 1625

Allowable Subject Matter


5. Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The closest art is Afonso (5801175) wherein a tricyclic compound useful as an inhibitor of farnesyl protein transferase is described (columns 1-6; column 135, example 246). The prior art examples are all directed to piperazinyl compounds. The instant compound is a piperidinyl compound having a nitrogen containing heterocyclic ring further substituted with an imidazolyl or pyridinyl containing moiety attached to the carbonyl on the piperidinyl ring. The closest prior art compound, example 246, is a piperazinyl compound, which further differs from the instant in the content of the R2 moiety on the piperazinyl ring. Motivation to modify the prior art compound to arrive at the instant invention via multiple changes is lacking.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 703-305-7247. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703-308-4698. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.


Evelyn Huang
Primary Examiner
Art Unit 1625

July 21, 2003